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Providing practical answers to practical questions for NOAC therapy

Jan Steffel

Department of Cardiology, Division of Electrophysiology and Pacing,
University Heart Center Zurich, Switzerland

Nine years ago, at the European Society of Cardiology Meeting 2009 in Barcelona, the first trial investigating a modern non-vitamin K antagonist oral anticoagulants (NOACs) in atrial fibrillation (AF) — the Re-LY trial comparing dabigatran to warfarin — was presented and published simultaneously in the "New England Journal of Medicine" [1]. Re-LY was followed by ROCKET-AF (with rivaroxaban) [2], ARISTOTLE (with apixaban) [3] and ENGAGE AF-TIMI 48 (with edoxaban) [4]. It was the start of a veritable paradigm shift in the prevention of stroke in AF; similar (if not better) efficacy with better safety (particularly regarding the most feared complication of intracranial hemorrhage) was nothing anybody would have anticipated beforehand.

Yet, the advent of these new drugs also meant the advent of new questions, many of which could not (yet) be answered readily by the landmark randomized clinical trials. What is the best "start-up" scheme if I want to newly start a patient on a NOAC? How do I best switch a patient from vitamin K antagonists (VKA)? How do we deal with dosing errors? What do we have to do in case of bleeding (the fear of the lack of a rapidly acting, specific antidote was enormous in the early days of NOACs — thereby ignoring that a rapidly acting, specific antidote also does not exist for VKA…)? When should we stop/when should we re-initiate NOACs around invasive procedures and operations? Can we cardiovert a patient under NOAC therapy? And many others. These questions, arising out of situations from "daily clinical practice" demanded for practical answers. The idea to the first "Practical Guide" of the European Heart Rhythm Association (EHRA) was born and ultimately realized by Hein Heidbüchel and his co-workers in 2013 [5]. The "EHRA Practical Guide" rapidly became a point of reference for many healthcare providers, from general practitioners to cardiologists, from specialized nurses to surgeons, when practical daily-life questions arose for which there was no answer (yet) from clinical trial data. In addition to these practical advice, the first edition of the Guide also already featured the "EHRA universal NOAC card". Purpose-equivalent to the international normalized ratio booklet of patients under VKA therapy, the main goals of this card were to inform healthcare providers of the therapy the patient is taking, especially in emergency situations where the patient may be unable to answer and, likely equally if not more important, to sensitize patients and make them aware that although they are not (or no longer) on VKA, this new medication is (a) important and should therefore (b) not be forgotten.

Over the years, several of the "data holes" which were dealt with initially in the Practical Guide 2013 were filled — e.g., with the first studies investigating the possibility to perform cardioversions in patients on NOACs, as well as important subanalyses on the use of NOACs in renal dysfunction. In addition, the availability of edoxaban after its presentation in November 2013 demanded for its inclusion in the Practical Guide. As such, an "Update" was published in 2015 acknowledging the developments in this rapidly moving field [6].

With the ever growing increase in the use of NOACs and — fortunately — undamped research interest in further refining the value and use of these drugs also in more complex scenarios, it was a matter of time until also the 2015 Update would become partially 'outdated'. As a result, another "update" was initiated in the summer of

Address for correspondence: Jan Steffel, MD, FESC, FEHRA, FHRS, Vice Chairman, Department of Cardiology, Senior Consultant, Division of Electrophysiology and Pacing, University Heart Center Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland, tel: +41 44 255 15 15, fax: +41 44 255 59 76, e-mail: j.steffel@gmx.ch

2017. However, during the planning phase it rapidly became clear that a simple "update" would likely not suffice this time given the exponential growth in knowledge and experience. As such, a fully reworked and expanded version of the EHRA Practical Guide was initiated and ultimately published in March 2018 (including 476 references, as compared to 101 in the 2013 edition) [7]. In the current issue of the "Cardiology Journal", Tomaszuk-Kazberuk et al. [8] summarize the main recommendations from this work. Several chapters were re-written thereby including newly available study data, such as the management of bleeding complications (with idarucizumab available since > 1 year, and andexanet alpha just around the corner) [9], the management of patients with AF and coronary artery disease (with PIONEER-AF [10] and Re-DUAL PCI [11] published, and ENTRUST and AUGUSTUS soon to be finished), and the management of an acute stroke in patients on NOACs (including the possibility to perform thrombolysis in selected individuals). At the same time, new and partially controversial issues were included such as "How to measure anticoagulant effect of NOACs" as well as a chapter on the rare indications, precautions, and potential pitfalls of plasma level measurements.

As we get more and more comfortable with the use of NOACs, many of the initially open questions could be answered. At the same time, we are moving out of our comfort zone and into treating more and more difficult patients. As a result, new questions arise: How can we use NOACs in severe renal insufficiency (and on dialysis)? What is the final verdict on triple therapy; will we need it at all, if so for whom? Will plasma level measurements really be of help — in emergency situations, in the peri-operative setting, in very special situations such as severe over- or underweight? And many more… it is highly likely that we will see some answers over the next years — followed for sure by a new version of the EHRA Practical Guide to keep on providing practical answers to practical questions in order to improve and optimize stroke prevention for the many patients with AF. It is a complex topic, with not a lot of easy answers; but clearly worthwhile investing time and effort into as the impact of correct and adequate anticoagulantion for our patients will likely be substantial.

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References

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361(12): 1139–1151, doi: 10.1056/NEJMoa0905561, indexed in Pubmed: 19717844.
2. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365(10): 883–891, doi: 10.1056/NEJMoa1009638, indexed in Pubmed: 21830957.
3. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365(11): 981–992, doi: 10.1056/NEJMoa1107039, indexed in Pubmed: 21870978.
4. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369(22): 2093–2104, doi: 10.1056/NEJMoa1310907, indexed in Pubmed: 24251359.
5. Heidbuchel H, Verhamme P, Alings M, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013; 15(5): 625–651, doi: 10.1093/europace/eut083.
6. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015; 17(10): 1467–1507, doi: 10.1093/europace/euv309, indexed in Pubmed: 26324838.
7. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018; 39(16): 1330–1393, doi: 10.1093/eurheartj/ehy136, indexed in Pubmed: 29562325.
8. Tomaszuk-Kazberuk A, Kołtowski Ł, Balsam P, et al. Use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation — Messages from the 2018 EHRA. Cardiol J. 2018; 25(4): 423–440, doi: 10.5603/CJ.2018.0080.
9. Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017; 377(5): 431–441, doi: 10.1056/NEJMoa1707278, indexed in Pubmed: 28693366.
10. Gibson CM, Mehran R, Bode C, et al. An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). Am Heart J. 2015; 169(4): 472–8.e5, doi: 10.1016/j.ahj.2014.12.006, indexed in Pubmed: 25819853.
11. Cannon CP, Bhatt DL, Oldgren J, et al. RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med. 2017; 377(16): 1513–1524, doi: 10.1056/NEJMoa1708454, indexed in Pubmed: 28844193.